Molecular events during selective ER-phagy

Bhaskara, R. M.,[1,2,3] Siggel, M.,[3] Moesser, M.K.,[3] Dikic, I.[1,2,4], and Hummer, G.[3,5]

[1]Institute of Biochemistry II (IBC2), Faculty of Medicine, Goethe University, 60590 Frankfurt am Main, Germany.2Buchmann Institute for Molecular Life Sciences (BMLS), Goethe University, 60438 Frankfurt am Main, Germany. [3]Department of Theoretical Biophysics, Max Planck Institute of Biophysics, 60438 Frankfurt am Main, Germany. [4]Max Planck Institute of Biophysics, 60438 Frankfurt am Main, Germany. 5Institute of Biophysics, Goethe University Frankfurt, 60438 Frankfurt am Main, Germany.

Living cells constantly remodel the shape of their lipid membranes. In the endoplasmic reticulum (ER), the reticulon homology domain (RHD) of the reticulophagy regulator 1 (RETR1/FAM134B) forms dense autophagic puncta that are associated with membrane removal by ER-phagy. Through molecular dynamics (MD) simulations of FAM134B in flat and curved membranes, we relate the dynamic RHD structure with its two wedge-shaped transmembrane helical hairpins and two amphipathic helices to FAM134B functions in membrane-curvature induction and curvature-mediated protein sorting. In MD simulations, FAM134B-RHD spontaneously forms clusters, driven in part by curvature-mediated attractions. At a critical size, as in a nucleation process, the FAM134B-RHD clusters amplifies the membrane shaping effect to induce the formation of membrane buds [2]. The kinetics of budding depends sensitively on protein concentration and bilayer asymmetry. Our MD simulations shed light on the role of FAM134B-RHD in ER-phagy and show that membrane simulations can be used to study various aspects of membrane remodelling, inaccessible to experiments.

[1] RM. Bhaskara et al., *Nat Commun* 10, 2370 (2019).

[2] M. Siggel et al., *J Phys Chem Lett* 12(7), 1926-1931 (2021).